Translation

PATENT COOPERATION TREATY

PCT/EP2003/009229

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/43161-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/009229	International filing date (*day/month/year*) 20 August 2003 (20.08.2003)	Priority date (*day/month/year*) 20 August 2002 (20.08.2002)
International Patent Classification (IPC) or national classification and IPC G01N 33/50		
Applicant GIESING, Michael		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 March 2004 (19.03.2004)	18 January 2005 (18.01.2005)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/009229

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-47, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-10, filed with the letter of 13 December 2004 (13.12.2004)

☒ the drawings:

pages 1/1, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/09229

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims	1-10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations

1. Cited Documents

Reference is made to the following documents:

D1: BOER JUDITH M ET AL: 'Identification and classification of differentially expressed genes in renal cell carcinoma by expression profiling on a global human 31,5000-element cDNA array' GENOME RESEARCH, COLD SPRING HARBOR LABORATORY PRESS, US, Vol. 11, No. 11, November 2001 (2001-11), pages 1861-1870, XP00221 5718, ISSN: 1088-9051

D2: SARTO C ET AL: 'MODIFIED EXPRESSION OF PLASMA GLUTATHIONE PEROXIDASE AND MANGANESE SUPEROXIDE DISMUTASE IN HUMAN RENAL CELL CARCINOMA' ELECTROPHORESIS, WEINHEIM, GERMANY, Vol. 20, No. 17, November 1999 (1999-11), pages 3458-3466, XP001176871, ISSN: 0173-0835

D3: WO 9629430 A (JOHN WAYNE CANCER INST; NAT GENETICS INST (US)), 26 September 1996 (1996-09-26)

D4: MOERK H ET AL: 'INVERSE MRNA EXPRESSION OF THE SELENOCYSTEINE-CONTAINING PROTEINS GI-GPX AND SEP IN COLORECTAL ADENOMAS COMPARED WITH ADJACENT

NORMAL MUCOSA' NUTRITION AND CANCER, LONDON, GB, Vol. 37, No. 1, 2000, pages 108-116, XP008014221, ISSN: 0163-5581

D5: SARTO C ET AL: 'RENAL CELL CARCINOMA AND NORMAL KIDNEY PROTEIN EXPRESSION' ELECTROPHORESIS, WEINHEIM, GERMANY, Vol. 18, No. 3/4, 1997, pages 599-604, XP008026280, ISSN: 0173-0835

D6: GLADYSHEV VADIM N ET AL: 'Contrasting patterns of regulation of the antioxidant selenoproteins, thioredoxin reductase, and glutathione peroxidase, in cancer cells' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, Vol. 251, No. 2, 20 October 1998 (1998-10-20), pages 488-493, XP002272356, ISSN: 0006-291X

D7: BRAVARD A ET AL: 'Modifications of the antioxidant enzymes in relation to chromosome imbalances in human melanoma cell lines' MELANOMA RESEARCH, Vol. 8, No. 4, August 1998 (1998-08),pages 329-335, XP002272357, ISSN: 0960-8931

D8: PESKIN A V ET AL: 'SUPER OXIDE DIS MUTASE AND GLUTATHIONE PER OXIDASE ACTIVITIES IN TUMORS' FEBS LETTERS, Vol. 78, No. 1, 1977, pages 41-45, XP002272358, ISSN: 0014-5793

D9: KAHLOS KATRIINA ET AL: 'Manganese superoxide dismutase in healthy human pleural mesothelium and in malignant pleural mesothelioma' AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, Vol. 18, No. 4, April 1998 (1998-04), pages 570-580, XP002272359, ISSN: 1044-1549

2. Novelty, Inventive Step and Industrial Applicability (PCT Article 33)

2.1. The present application describes a method for examining bodily fluids for cancer cells.

Document D1 describes the examination of tissues in order to measure the expression of manganese superoxide dismutase and glutathione peroxidase in tumor tissue. Although D1 assumes that these proteins can be used as markers for the diagnosis of renal cell carcinoma (D1, page 3458), this document does not describe a method of this type for examining bodily fluids for cancer cells.

Document D2 describes the examination of cancer and normal cells in order to measure the expression of glutathione peroxidase and superoxide dismutase (D2, figure 5). Expression profiles are described that are intended to be used to classify renal cell carcinoma (page 1867). However, document D2 does not describe a method that employs these markers to examine bodily fluids for cancer cells.

Therefore, claim 1 appears novel with respect to documents D1 and D2. The same applies to dependent claims 2-8.

The prior art (D1 to D9) also fails to disclose the following features: an analysis kit containing means for identifying at least one manganese superoxide dismutase gene, at least one thioredoxin reductase gene and at least one glutathione peroxidase gene (claims 9 and 10).

Therefore, the subject matter of claims 1-10 is novel (PCT Article 33(2)).

2.2. Document D1 describes the examination of tissues in order to measure the expression of manganese superoxide dismutase and glutathione peroxidase genes.

As mentioned above, D1 indicates that these proteins can be used as markers for the diagnosis of renal cell carcinoma (D1, page 3458). The present application differs from D1 in that the aforementioned markers (manganese superoxide dismutase and glutathione peroxidase) are used to identify cancer cells in bodily fluids.

The technical effect of this method is that it is possible to detect cancer cells in bodily fluids, including circulating cancer cells, which can differ from those of the primary tumor. In addition, the claimed method is largely independent of the tumor type and is highly reliable.

The technical problem addressed by the application can thus be seen as that of providing a reliable method of detecting cancer cells in bodily fluids that is not limited by the tumor type.

There is nothing in document D1 that could induce a person skilled in the art to develop a method of this type. Therefore, the subject matter of claim 1 and of dependent claims 2-8 involves an inventive step (PCT Article 33(3)).

2.3. Claim 9 describes an analysis kit containing means for identifying at least three genes, namely a manganese superoxide dismutase gene, a thioredoxin reductase gene and a glutathione peroxidase gene. Documents D1 and D2 describe components that can be used to identify two of these markers.
However, neither D1 nor D2 discloses an analysis kit containing all three components, nor do said documents include any indication of a possible

combination of precisely these three marker molecules.
An analysis kit according to claims 9 and 10 is thus not disclosed or suggested by D1 or D2, alone or in combination.
It follows then the advantageous use of a combination of said three marker molecules, as represented on page 37 of the description, is also neither disclosed nor suggested.
Therefore, claims 9 and 10 satisfy the requirements of PCT Article 33(3).

2.4. The subject matter of claims 1-10 appears to be industrially applicable.

3. Further Observations:

3.1. The application must be self-explanatory and references cannot be incorporated as part of the description (e.g. page 25 of the description).

3.2. The expression "cancer cell" is defined on page 3 so as to also include cells containing precursors of cancer cells. It is unclear whether this definition is generally common. The exact definition of the term should be clear (included) in claim 1 in order to satisfy the requirements of PCT Article 6.

3.3. The expression "in particular" in claim 8 does restrict the scope of protection of the claim and results in a lack of clarity (PCT Article 6).

3.4. The embodiment of the invention (treatment of cancer) described on page 27 is not covered by the current claims. This inconsistency between the claims and the

description leads to doubt as to the subject matter for which protection is sought, and consequently the claims are not clear (PCT Article 6). The applicant should therefore remedy this inconsistency, namely by clarifying that the methods of treatment represented are merely illustrative and are not being claimed.

3.5. Contrary to PCT Rule 5.1(a)(ii), the description does not cite documents D1 to D9 or indicate the relevant prior art disclosed therein.